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Part II

**Department of
Health and Human
Services**

Food and Drug Administration

**External Analgesic Drug Products for
Over-the-Counter Human Use; Tentative
Final Monograph**

misbranded (monograph conditions) will be effective 12 months after the date of publication of the final monograph in the Federal Register. On or after that date, no OTC drug products that are subject to the monograph and that contain nonmonograph conditions, i.e., conditions that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce unless they are the subject of an approved new drug application. Further, any OTC drug products subject to this monograph that are repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

In the advance notice of proposed rulemaking for OTC external analgesic drug products (published in the Federal Register of December 4, 1979 (44 FR 69768)), the agency suggested that the conditions included in the monograph (Category I) be effective 30 days after the date of publication of the final monograph in the Federal Register and that the conditions excluded from the monograph (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph, regardless of whether further testing was undertaken to justify their future use. Experience has shown that relabeling of products covered by the monograph is necessary in order for manufacturers to comply with the monograph. New labels containing the monograph labeling have to be written, ordered, received, and incorporated into the manufacturing process. The agency has determined that it is impractical to expect new labeling to be in effect 30 days after the date of publication of the final monograph. Experience has shown also that if the deadline for relabeling is too short, the agency is burdened with extension requests and related paperwork.

In addition, some products have to be reformulated to comply with the monograph. Reformulation often involves the need to do stability testing on the new product. An accelerated aging process may be used to test a new formulation; however, if the stability testing is not successful, and if further reformulation is required, there could be a further delay in having a new product available for manufacture.

The agency wishes to establish a reasonable period of time for relabeling and reformulation in order to avoid an unnecessary disruption of the marketplace that could not only result in economic loss, but also interfere with consumers' access to safe and effective drug products. Therefore, the agency is proposing that the final monograph be effective 12 months after the date of its publication in the Federal Register. The agency believes that within 12 months after the date of publication most manufacturers can order new labeling and have their products in compliance in the marketplace. However, if the agency determines that any labeling for a condition included in the final monograph should be implemented sooner, a shorter deadline may be established. Similarly, if a safety problem is identified for a particular nonmonograph condition, a shorter deadline may be set for removal of that condition from OTC drug products.

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for-data notice published in the Federal Register of July 21, 1972 (37 FR 14633) or to additional information that has come to the agency's attention since publication of the advance notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch.

In the Federal Register of September 7, 1982 (47 FR 39412), FDA issued a notice of reopening of the administrative record for OTC external analgesic drug products to allow for consideration of the Miscellaneous External Panel's recommendations on external analgesic drug products used for the treatment of diaper rash, for prevention of poison ivy, oak, and sumac, for the treatment of fever blisters, as male genital desensitizers, as astringents, and as insect bite neutralizers. The agency will address the use of external analgesic active ingredients for these uses in this rulemaking in a future issue of the Federal Register.

I. The Agency's Tentative Conclusions on the Comments

A. General Comments on External Analgesic Drug Products

1. One comment contended that OTC drug monographs are interpretive, as opposed to substantive, regulations. The comment referred to statements on this issue submitted earlier to other OTC rulemaking proceedings.

The agency addressed this issue in paragraphs 85 through 91 of the preamble to the procedures for classification of OTC drug products,

published in the Federal Register of May 11, 1972 (37 FR 9464) and in paragraph 3 of the preamble to the tentative final monograph for antacid drug products, published in the Federal Register of November 12, 1973 (38 FR 31260). FDA reaffirms the conclusions stated there. Subsequent court decisions have confirmed the agency's authority to issue substantive regulations by rulemaking. See, e.g., *National Nutritional Foods Association v. Weinberger*, 512 F. 2d 688, 696-98 (2d Cir. 1975) and *National Association of Pharmaceutical Manufacturers v. FDA*, 487 F. Supp. 412 (S.D.N.Y. 1980), *aff'd*, 637 F. 2d 687 (2d Cir. 1981).

2. One comment stated that two products, both containing the active ingredients camphor, menthol, eugenol, and eucalyptus oil, had "grandfathered" status under section 201(p)(1) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(p)(1)). The comment pointed out that, although these products do not comply with the Panel's recommended monograph because of their high level of camphor, they have been continuously marketed since 1923. The comment argued that, because of the grandfather status, the conclusions of the OTC drug review should not be applicable to these products.

The agency points out that after this comment was submitted the two products were reformulated to reduce the concentration of camphor from 25 percent to 11 percent, in conformance with the Panel's recommendations. Consequently, the question of grandfather status for those 25 percent products is moot.

The "grandfather" clause in the act of 1938 is not applicable to any drug relabeled or reformulated after June 25, 1938. Similarly, a drug marketed before the 1962 amendments to the act, which was not then a new drug or covered by a new drug application, is subject to the provisions of these amendments regarding effectiveness if the drug has been reformulated or relabeled. The 1938 and 1962 grandfather clauses apply only to the new drug provisions of the act and not to the adulteration or misbranding provisions. The OTC drug review was designed to implement both the misbranding and the new drug provisions of the act. Therefore, the grandfather clauses do not preclude the agency from reviewing any currently marketed OTC drug, regardless of whether it has grandfather protection from the new drug provisions, in order to ensure that the drug is not misbranded.

B. Comments on External Analgesic Ingredients

3. A number of comments expressed opinions on the Panel's recommended switch of hydrocortisone to OTC marketing status. The comments that favored OTC marketing pointed out the long history of experience with this drug as well as the savings to the consumer from OTC availability. Several comments stated that the recommended OTC indications would permit informed and prudent use of hydrocortisone products by providing consumers with appropriate examples of self-diagnosable conditions for which hydrocortisone products provide appropriate therapy. Opposing comments stated that hydrocortisone is likely to be used inappropriately because the average consumer is unable to distinguish between a simple rash and such skin conditions as herpes simplex, scabies, seborrheic dermatoses, and tinea cruris (jock itch). The comments added that inappropriate treatment and delay in diagnosis might cause the conditions to spread or become worse at considerable cost to the consumer.

The agency agrees with the Panel that the OTC marketing of hydrocortisone is of significant benefit to consumers because it provides them with an effective drug for self-treatment of certain minor skin irritations. The indications for OTC use are for self-limiting, self-diagnosable conditions. The warning proposed in § 348.50(c)(1)(iii) of this tentative final monograph, "If condition worsens, or if symptoms persist for more than 7 days or clear up and occur again within a few days, discontinue use of this product and consult a" (select one of the following: "physician" or "doctor,") is intended to prevent unlimited consumer use of these products for serious conditions that require professional treatment. (See comment 27 below.) The agency tentatively concludes that hydrocortisone is safe and effective for its labeled OTC uses and that the benefits of OTC availability outweigh any potential misuse that may occur.

4. Two comments form the same source requested that the maximum allowable concentration of camphor recommended by the Panel in § 348.10 (a)(3) be raised from 11 to 25 percent. The comments cited a study to determine the dermal irritancy and possible toxicity of 25 percent camphor and argued that the results of the study justify this higher concentration (Ref. 1). The comments also cited the long marketing history of a product containing a higher concentration of

camphor with no reports of major problems.

The agency disagrees with the comments. The study submitted by one comment to justify raising the camphor limit to 25 percent used traditional Draize procedures in which a product containing 25 percent camphor was applied to rabbits' skin for 21 consecutive days (Ref. 1). This is a standard method of testing topical irritancy. The Panel stated that camphor in concentrations above 11 percent is not harmful when used topically, but the Panel was concerned about poisoning if products containing higher concentrations were accidentally ingested (44 FR 69803). Eleven percent was chosen as a maximum limit by the Panel because higher concentrations are not any more effective as counterirritants, but can cause more serious adverse reactions if accidentally ingested. The agency concurs with the Panel's conclusion.

Furthermore, the product discussed in the comment has been reformulated, lowering the camphor concentration from 25 percent to 11 percent (Ref. 2). The agency is not aware of counterirritant products containing more than 11 percent camphor now on the OTC market; therefore, the agency finds no reason to consider camphor concentrations greater than 11 percent any further in this document.

References

- (1) Comment No. C00027, Docket No. 78N-0301, Dockets Management Branch.
- (2) Food and Drug Administration, "Drug Product Listing for Tiger Balm Ointment," Haw Par Brothers International Limited, January 15, 1980 and January 9, 1981, included in OTC Volume 06BTfM.

5. A number of comments objected to the recommendations of the Miscellaneous External Panel, included in the rulemaking for external analgesic drug products on September 26, 1980 (45 FR 63878), that the quantity of camphor in OTC drug products be limited to 2.5 percent, that no package contain more than 360 milligrams (mg) of camphor, and that safety packaging be used. One comment argued that it is unacceptable to limit household drug products to 360 mg of camphor per container, which would be the equivalent of a spoonful-size container for many products, on the basis that accidental ingestion of larger amounts may cause toxic effects. Another comment argued that the Miscellaneous External Panel was wrong in basing its calculation of the toxic dose of 30 milligrams/kilogram (mg/kg) on a single report of death following ingestion by a 150-pound man of 2 grams (g) of camphor. The comment

argued that other reports place the toxic dose higher than 30 mg/kg and that most of the reported cases of camphor poisoning may not be true poisonings with toxic signs and symptoms. The comment added that of 542 cases of camphor poisoning cited by the Poison Control Center for 1974, only 101 reported any symptoms, and of this number only 77 were hospitalized. Several comments pointed out that there are no reported fatalities associated with products containing 11 percent or less camphor, and that most of the poisonings described by the Miscellaneous External Panel were due to ingestion of camphorated oil, which contains 20 percent camphor in oil. One comment pointed out that limiting the package size to avoid potential misuse would be a proper consideration for the Consumer Product Safety Commission under the provisions of the Poison Prevention Packaging Act, and should not be incorporated into an OTC drug monograph. Another comment argued that there was no justification for applying the recommendations of the Miscellaneous External Panel to nonliquid formulations of camphor because of the lower risk of ingestion of these formulations.

The agency notes that the Topical Analgesic Panel considered various comments, reports, and editorials submitted to it concerning the toxicity and frequency of poisonings from camphor-containing preparations, particularly in children because that population has the highest incidence of such toxicity. The Panel concluded that the cases of accidental ingestion of products containing 11 percent or less camphor by children rarely resulted in severe adverse reactions and that current regulations and labeling requirements are adequate. The agency has reviewed both panels' recommendations and the adverse reaction reports for products containing camphor and concludes that, at this time, there is no need to limit camphor content to 360 mg per package for products covered by this tentative final monograph. The camphor concentration is being limited to 11 percent or lower as recommended by the Topical Analgesic Panel. (See comment number 4 above.) A final rule declaring camphorated oil products to be new drugs and misbranded was published in the Federal Register of September 21, 1982 (47 FR 41716).

There are few reports of adverse reactions from ingestion of solid dosage forms containing camphor; however, the agency believes that safety packaging of liquid products would reduce the risk

that children might ingest these products. The agency strongly recommends that manufacturers voluntarily package such products in child-resistant containers. In addition, these products must bear the warning: "For external use only." The agency recommends that manufacturers voluntarily print this warning in a larger size print and/or in a different color from other information on the label to draw consumers' attention to it. The agency believes that if manufacturers take these additional steps, the number of accidental ingestions can be reduced.

6. One comment requested clarification of the gap between the dosage ranges for menthol as an analgesic, anesthetic, or antipruritic (0.1 to 1.0 percent) and as a counterirritant (1.25 to 16 percent).

The Panel proposed two dosage ranges to emphasize the distinction between the two different OTC uses of menthol and the different labeling associated with each use. The agency concurs with the Panel's recommendations of these dosage ranges.

7. Two comments submitted data on the effectiveness of trolamine salicylate (formerly triethanolamine salicylate) as a topical analgesic. Based on these data, one of the comments suggested that the monograph include a class of external analgesics that "act upon painful structures below the skin by absorption of the active ingredient directly into subcutaneous structures" and that trolamine salicylate be placed in this class. The comment also suggested the following indications for this class: "For the temporary relief of minor aches and pains of muscles and joints. Also as a topical adjunct for pain due to arthritis and rheumatism." Both comments requested that trolamine salicylate be placed in Category I based on the data submitted.

The agency has reviewed the data submitted and concludes that they are not sufficient to support general recognition of effectiveness for trolamine salicylate as an OTC external analgesic.

The studies by Ehrlich (Ref. 1), Charles (Ref. 2), Brown (Ref. 3), and Roth (Ref. 4) were randomized, double-blind, crossover evaluations of 10 percent trolamine cream versus placebo. None of these studies reported any significant differences between active drug and placebo for any of the measurements recorded.

A double-blind, placebo-controlled, crossover study by Batterman and Sanders (Ref. 5) evaluated the effect of 10 percent trolamine salicylate in relieving the pain of arthritis of the hand

in two groups of patients. In one group there was subjective evidence only of superiority of the trolamine cream over placebo, whereas measurable indicators such as hand-grip strength and finger-joint circumference showed no statistically significant improvement. In the other group, trolamine salicylate showed no superiority over the placebo in any of the three measurable criteria. Thus, the results of this study do not indicate any clear superiority of trolamine salicylate over placebo.

Golden (Ref. 6) compared topically applied 10 percent trolamine salicylate cream to oral aspirin in a double-blind parallel study of the relief of rheumatic pain, concluding that the topically applied trolamine salicylate was at least as effective as aspirin in providing pain relief. However, the study design has several deficiencies. History of aspirin use, effective dose, and adverse reactions were not recorded for each subject. Without this information about aspirin response, there is a potential for bias against aspirin in treatment response and adverse reactions.

Altschuler and Golden (Ref. 7) studied 10 percent trolamine salicylate cream in patients with musculoskeletal pain. Of the six results reported, only one was statistically significant. Furthermore, the selective reporting of these six results renders this report uninformative, and no conclusions can be made concerning the effectiveness of trolamine salicylate.

Patel and Chappelle (Ref. 8) reported results observed from unblinded and uncontrolled clinical trials of trolamine salicylate in two French hospitals. The results cannot be assessed because of the lack of a control group.

The comments also included information on the penetrating properties of trolamine salicylate, including in vivo studies in animals, a boiled-egg technique said to demonstrate penetration through protein, and a cup method to demonstrate penetration through muscle and connective tissue. This information is not adequate or suitable to demonstrate effectiveness of trolamine salicylate as a topical analgesic.

Because the submitted information fails to demonstrate that this ingredient would be effective for application at the site of pain or for any use as an external analgesic, the agency does not agree with the comments that trolamine salicylate should be placed in a new class of external analgesic drug products. Trolamine salicylate remains in Category III as an anesthetic, analgesic, and antipruritic in this tentative final monograph. The agency's detailed review and evaluation of the studies submitted are on file in the

Dockets Management Branch (Refs. 9 and 10). In response to the agency's review, a comment submitted additional data on trolamine salicylate (Ref. 11). These data were submitted after the administrative record had closed and will be addressed after publication of this tentative final monograph.

References

- (1) Ehrlich, G. E., "Myoflex Creme in Patients with Chronic Musculoskeletal Complaints," Comment No. C0008, Docket No. 78N-0301, Dockets Management Branch.
- (2) Charles, A. A., "Myoflex Creme in the Treatment of Chronic Musculoskeletal Complaints," Comment No. C0008, Docket No. 78N-0301, Dockets Management Branch.
- (3) Brown, B., "Myoflex/Chronic Musculoskeletal Complaints," Comment No. C0008, Docket No. 78N-0301, Dockets Management Branch.
- (4) Roth, S. H., "Myoflex Arthritis Study," Comment No. C0008, Docket No. 78N-0301, Dockets Management Branch.
- (5) Batterman, R. C., and J. F. Sanders, "Myoflex Creme in Patients with Arthritic Involvement of the Hand," Comment No. C00008, Docket No. 78N-0301, Dockets Management Branch.
- (6) Golden, E. L., "A Double-Blind Comparison of Orally Ingested Aspirin and a Topically Applied Salicylate Cream in the Relief of Rheumatic Pain," *Current Therapeutic Research*, 24:524-529, 1978.
- (7) Altschuler, S., and E. Golden, "Double-Blind Comparison of Triethanolamine Salicylate with a Placebo for Pain Relief from Muscular Skeletal Pain," Comment No. C00007, Docket No. 78N-0301, Dockets Management Branch.
- (8) Patel, A., and P. A. Chappelle, "Summary of TEA Clinical Trials in France, 1976-77," Comment No. C0007, Docket No. 78N-0301, Dockets Management Branch.
- (9) Letter from W. E. Gilbertson, FDA, to W. L. Myers, Warren-Teed Laboratories, June 19, 1981, coded LET003, Docket No. 78N-0301, Dockets Management Branch.
- (10) Letter from W. E. Gilbertson, FDA, to E. L. Steinberg, Thompson Medical Co., June 19, 1981, coded LET 004, Docket No. 78N-0301, Dockets Management Branch.
- (11) Comment Nos. CP, SUP002, CR001, AMD, and AMD002, Docket No. 78N-0301, Dockets Management Branch.

Comments on Combination Products

8. One comment argued against the Category III classification of a combination product containing two Category I ingredients and one ingredient classified in Category III for effectiveness. The comment objected to the entire product being placed in Category III, according to the Panel's recommendations, when there has been no question of the product's safety or the effectiveness of the two Category I active ingredients. The comment argued that rather than require reformulation of the product, which would require research, stability testing, and quality

control testing, relabeling to indicate that the Category III ingredient is an inactive ingredient should be permitted.

The agency has published a proposed rule dealing specifically with the use of inactive ingredients in OTC drug products. (See the Federal Register of April 12, 1977 [42 FR 19156].) The proposal identified suitable physical or technical functions (e.g., denaturing agents, emollients, dispersing agents) that an inactive ingredient must perform to be regarded as appropriate for use in OTC drug products. The rule proposed to preclude the retention and redesignation of an active ingredient as an inactive ingredient unless it performs one of these functions. Although this proposal has not yet been published as a final rule, the agency does not sanction arbitrary redesignation to inactive status of ingredients that were submitted as active ingredients and for which data are insufficient to show effectiveness. If such ingredients were retained in a formulation and designated inactive, consumers would be needlessly exposed to them without any corresponding benefit. Many ingredients that are generally recognized as safe are still capable of causing side effects, allergic reactions, etc.

Paragraph 5 of the agency's "General Guidelines for OTC Drug Combination Products" (Ref. 1) provides that "In some cases an ingredient may be appropriate for use only in a specific combination or data may be available only to support the use of the ingredient in combination but not as a single ingredient. In such cases the ingredient will be placed in Category I for use only in permissible combinations and not as a single ingredient." The comment did not mention the specific ingredients contained in its product, nor did it submit any data to support the use of the Category III ingredient in the combination product only. If data are submitted to support the use of the ingredient in the combination, i.e., showing contribution to the claimed effect, as required by 21 CFR 330.10(a)(iv), then it could be classified as Category I for use in the specific combination but not as a single ingredient.

Reference

(1) Food and Drug Administration. "General Guidelines for OTC Drug Combination Products." September, 1978. Docket No. 78D-0322, Dockets Management Branch.

9. One comment, from the author of the Panel's minority report on combination products (44 FR 69787-69790), suggested a number of changes in the minority report, which, the

comment stated, would make it consistent with the agency's general guidelines for OTC drug combination products (Ref. 1), which were published after the Panel had adopted its report. The comment requested that this minority report, with suggested revisions, replace the combination policy recommended by the majority of the Panel members in § 348.20, adding that such a replacement would eliminate the provisions of the majority report that have no therapeutic or scientific basis.

The agency accepts the changes in the minority report and has considered these revisions along with the combination policy developed by the majority of the Panel and other comments received (see comment 8 above and comments 10, 11, and 12 below). The agency's proposed regulations for combinations of OTC external analgesic active ingredients, based on the consideration of all these factors, are set forth in § 348.20 of this tentative final monograph. The agency believes these proposed regulations have therapeutic and scientific bases and are consistent with the regulations governing combinations of OTC active ingredients in § 330.10(a)(4)(iv) and the agency's supplementary guidelines (Ref. 1). Therefore, the agency sees no reason for the revised minority report to replace the combination policy recommended by the majority of the Panel.

Reference

(1) Food and Drug Administration. "General Guidelines for OTC Drug Combination Products." September 1978. Docket No. 78D-0322, Dockets Management Branch.

10. One comment supported the combination policy recommended by the majority of the Panel (44 FR 69785), but objected to limiting combination products to no more than one active ingredient from each specified group in § 348.20 (a), (b), and (c). The comment requested that more than one ingredient from each group be permitted provided that the combination conforms with the OTC drug review regulations (§ 330.10(a)(4)(iv)).

The combination policy in § 330.10(a)(4)(iv), as supplemented by the agency's general guidelines for OTC drug combination products (Ref. 1), specifies the criteria for OTC combination drug products. The agency's guidelines state that ingredients from the same therapeutic category that have different mechanisms of action may be combined to treat the same symptoms or condition if the combination meets the OTC combination policy in 21 CFR 330.10(a)(4)(iv) in all respects and the

combination is, on a benefit-to-risk basis, equal to or better than each of the active ingredients used alone at its therapeutic dose. The guidelines also state that Category I active ingredients from the same therapeutic category that have the same mechanism of action should not ordinarily be combined unless there is some advantage over the single ingredient in terms of enhancing effectiveness, safety, patient acceptance, or quality of formulation. Thus, the combination policy in § 330.10(a)(4)(iv) and the agency's supplementary guidelines do not limit the number of ingredients from the same pharmacologic group that may be combined, provided data are presented to show that the combination meets the necessary criteria. The comment, however, did not submit any such data. Combinations containing ingredients from the same pharmacologic group will be permitted if adequate data are presented to the agency, and § 348.20 will be amended accordingly.

Reference

(1) Food and Drug Administration. "General Guidelines for OTC Drug Combination Products." September 1978. Docket No. 78D-0322, Dockets Management Branch.

11. One comment requested that hydrocortisone be allowed in combination with the ingredients in group II A (the "caine" type analgesics) listed at 44 FR 69786. The comment argued that to prohibit such combinations is a departure from the combination policy set forth in 21 CFR 330.10(a)(4)(iv), that the marketing history of these combinations in prescription products does not show any adverse reactions, and that the effectiveness of such combinations is well documented by the effectiveness of the individual ingredients. Another comment requested that hydrocortisone combinations not be classified in Category II because there are various other pharmacological categories of drugs that can properly be combined with hydrocortisone, such as antifungal agents or skin protectants. The comment requested that consideration be given to including under § 348.20(b) combinations of hydrocortisone with the other ingredients listed under recommended § 348.10(b).

The agency does not agree with the comments that hydrocortisone should be allowed to be marketed OTC in combination with other external analgesic active ingredients at this time. The "caine"-type analgesics have indications similar to hydrocortisone, but have different mechanisms of action.

FDA's General Guidelines for OTC Drug Combination Products allow for such combinations if the combination is on a benefit-to-risk basis equal to or better than each active ingredient used alone at its therapeutic dose (Ref. 1). However, no evidence has been submitted demonstrating that the combination of hydrocortisone with a "caine" analgesic would meet this criterion. If such data are received, the agency will consider an addition to § 348.20.

The agency notes that the Panel's recommended monograph for skin protectant drug products, published in the Federal Register of August 4, 1978 (43 FR 34628), provides for certain skin protectants to be labeled for the symptoms of oozing or weeping due to poison oak or poison ivy (§ 347.50(b)(6)), while the recommended monograph for external analgesic drug products includes relief of minor skin irritations, itching, and rashes due to poison oak or poison ivy in the label indication for hydrocortisone (§ 348.50(b)(3)). The agency therefore will consider the combination of a skin protectant with hydrocortisone for treatment of the symptoms of poison oak or poison ivy if data to support such a combination are submitted. Combinations of antifungal agents and hydrocortisone were considered by the Antimicrobial II Panel in its report on antifungal drug products, published in the Federal Register of March 23, 1982 (47 FR 12480). Such combinations will be addressed in that rulemaking.

Reference

(1) Food and Drug Administration, "General Guidelines for OTC Drug Combination Products," September 1978, Docket No. 78D-0322, Dockets Management Branch.

12. One comment stated that the Panel's recommendations in § 348.20(a) would not allow a combination of camphor and menthol, but would allow a combination of camphor, menthol, and certain other external analgesic active ingredients. The comment requested that § 348.20(a) be amended to allow combination products containing only camphor and menthol as the active ingredients.

The agency agrees with the comment that the monograph should provide for combination products containing camphor and menthol as the only active ingredients. The omission of this combination appears to have been an oversight. Accordingly, the agency is proposing to amend § 348.20 by adding new paragraph (a)(6) to read as follows:

(6) Camphor identified in § 348.12(b)(1) may be combined with menthol identified in § 348.12(b)(2).

13. One comment stated that the Panel's recommended concentration limits for phenol and camphor are not appropriate for a product containing a complex of the two ingredients and requested that 4.7 percent phenol combined with 10.8 percent camphor in light mineral oil be permitted in analgesic, anesthetic, and antipruritic drug products. The comment argued that the clathrate complex that is formed when camphor is combined with phenol significantly reduces the available phenol and camphor. The comment submitted data to show that the combination is less irritating than the same amount of phenol or camphor alone and added that, based on actual consumer use, a product containing this camphor/phenol combination produces remarkably little irritation or erythema (Ref. 1).

Another comment from a manufacturer of products containing camphorated metacresol, which is composed of camphor and metacresol in a 3-to-1 ratio, objected to the Category III status of 1 to 3 percent camphorated metacresol and the Category II status of camphorated metacresol over 3 percent concentration (Ref. 2). The comment explained that the action of cresol is not associated with protein binding and would not therefore encourage continued release of "free" metacresol. The comment stated that toxic doses of cresol far exceed the quantities released even by products containing 88 percent camphorated metacresol. The comment argued that its products, which contain from 4 to 88 percent camphorated metacresol (composed of 1 to 22 percent metacresol and 3 to 86 percent camphor), should be placed in Category I based on their long history of safe use, and on data showing that metacresol is the least toxic of the cresols, that metacresol is less toxic than phenol, and that the rate of absorption of metacresol depends more on the area covered than on the concentration (Ref. 3).

The Agency agrees with the comment and the Panel that phenol combined with camphor can be safely used at a higher concentration than phenol used alone. Since the Panel adopted its report, the agency has verified that the amount of free phenol is reduced when camphor and phenol are combined (Ref. 4). Although the Panel recommended in its monograph a maximum level of 2 percent phenol and did not provide for a different concentration of phenol in combination with camphor, the Panel stated in its report that "When camphor is added to phenol, a liquid form. This reduces the severity of the topical reaction and the absorption of phenol . . ." (44 FR 69833). In addition, the

summary minutes of the Panel's seventh meeting indicate that the Panel intended to place the combination of 4.7 percent phenol and 10.8 percent camphor into Category I for both safety and effectiveness (Ref. 5). The Panel concluded that both phenol and camphor as single ingredients are Category I. The Panel's Category I recommendation for the complex was inadvertently omitted from its recommended monograph.

Another panel, the Advisory Review Panel on OTC Antimicrobial Drug Products (Antimicrobial I Panel), stated that "when camphor is used with phenol in an oil formulation, the concentration of phenol should be no more than 5 percent" (39 FR 33133). In reviewing data on camphor/phenol combinations, the Antimicrobial I Panel concluded that "the presence of camphor also retards the absorption of phenol after topical application. A 1-hour exposure of the rat tail to a 4.8 percent aqueous phenol solution resulted in the absorption of 71 mg of phenol; whereas, the exposure to 10.9 percent camphor combined with 4.5 percent phenol resulted in the absorption of only 16 mg phenol" (39 FR 33122). The agency concluded in the tentative final monograph for OTC topical antimicrobial drug products "that the total concentration of phenol in powders and in aqueous, alcoholic or oil formulations be restricted to less than 1.5 percent. When camphor is used with phenol in an oil formulation, the concentration of phenol should be no more than 5 percent" (43 FR 1238). To reduce the irritating potential of phenol when concentrations of 4.7 percent are used, camphor must be present in excess of that concentration (Refs. 1 and 4). Accordingly, the agency is proposing that 4.7 percent phenol, when it is combined with 10.8 percent camphor, be included in the tentative final monograph. The agency is proposing to add new paragraph (b)(4) to § 348.20 to read as follows:

(4) Camphor and phenol identified in § 348.10(b)(3) and (8) may be combined in a light mineral oil, USP vehicle.

At this time, the agency is proposing to restrict the vehicle to light mineral oil, USP, because safety and effectiveness have been established in that vehicle only. Different vehicles can change the irritating properties of the combination (Refs. 6 and 7). There is evidence that vehicles containing glycerin or gelling agents such as silicon dioxide can increase the irritating properties of the combination (Ref. 7). Therefore, all other vehicles are classified as Category III at this time. Interested persons may submit data to support the use of other vehicles.

Regarding camphorated metacresol, the Panel stated that it is either a "complex" formed by the interaction of camphor with metacresol or a solution of the cresol in camphor. Since the panel adopted its report, the agency has determined that metacresol behaves similarly to phenol with respect to bonding with camphor and therefore can be considered a "complex" and categorized as camphorated metacresol (Ref. 4).

As a single ingredient, metacresol was not reviewed by the Panel. However, it has been shown to be somewhat less toxic than phenol based on the following LD₅₀ data (Ref. 3):

LD₅₀ METACRESOL AND PHENOL (IN G/KG)

Species	Route	Meta-cresol	Phenol
Rabbit	Subcutaneous	0.50	0.50
Cat	Subcutaneous	0.18	0.08
Mouse	Subcutaneous	0.45	0.35
Cat	Intravenous	0.28	0.18

The results indicate that the range of acute toxicity of metacresol is similar to phenol.

Based on the available information, which includes recognition of the combination of phenol and camphor as Category I, data showing metacresol is equal to or less toxic than phenol, and the new data showing that metacresol bonds to camphor similarly to phenol, the agency concludes that camphorated metacresol is Category I but only when prepared from camphor and metacresol combined in a 3-to-1 ratio not to exceed a concentration of 10.8 percent camphor. Based on a 3-to-1 ratio of camphor to metacresol with a limit of 10.8 percent camphor, the upper limit for metacresol is 3.6 percent. This 3-to-1 ratio results in reduced irritation (Ref. 2). The agency is proposing a lower limit of 1 percent metacresol based on information on marketed products submitted by the comment (Ref. 2). Accordingly, the agency is proposing to add new paragraph (b) to § 348.3, *Definitions*, in this tentative final monograph to read as follows:

(b) *Camphorated metacresol*, a complex consisting of camphor and metacresol combined in a ratio of 3 parts camphor to 1 part metacresol.

The comment did not provide sufficient data to establish general recognition of safety of a concentration of metacresol greater than 3.6 percent when this ingredient is combined with camphor. The studies reviewed by the Panel and the studies submitted by the comment (Ref. 2) were very limited in scope and are inadequate to demonstrate safety of higher concentrations. Most of the animal

toxicity studies tested only one animal, observed the animal only for a short period of time, and did not include a detailed examination of the animal following drug application. The comment's statements about rate of release of metacresol are unproven because the comment submitted no information on the quantity of metacresol released under the conditions of use. The comment also did not submit any data to support the safety of concentrations of camphor above 10.8 percent.

In regard to the comment's claim of "long history of safe use," marketing history alone cannot be regarded as adequate proof of safety. The safety of camphorated metacresol as an external analgesic above the established dosage (not to exceed 3.6 percent metacresol and 10.8 percent camphor) has not been established, and therefore concentrations above this dosage remain in Category III.

References

- (1) Comment No. C0013, Docket No. 78N-0301, Dockets Management Branch.
- (2) Comment No. C0006, Docket No. 78N-0301, Dockets Management Branch.
- (3) Public Health Service, The National Institutes of Health, "Phenol and Its Derivatives: The Relation Between Their Chemical Constitution and Their Effect on the Organism," by W. F. Von Oettingen, National Institutes of Health Bulletin, No. 190, pp. 59-71, 1949.
- (4) "OTC Drugs," (Camphor and Phenol), Semiannual Report of Laboratory Activities, Bureau of Drugs, Food and Drug Administration, October 1981 to July 1982, Docket No. 78N-0301, Docket Management Branch.
- (5) Summary minutes of Seventh Meeting of the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products, p. 4, January 30 and 31, 1974, included in OTC Volume 06BPA2.
- (6) Deichmann, W. B., T. Miller, and J. B. Roberts, "Local and Systemic Effects Following Application of Dilute Solutions of Phenol in Water and in Camphor-Liquid Petrolatum on the Skin of Animals," *Archives of Industrial Hygiene and Occupational Medicine*, 2:454-461, 1950.
- (7) Sterling-Winthrop Research Institute, "Eye and Skin Irritation Study with Camphor-Phenique Gel in the Rabbit," Table III, unpublished study, September 28, 1977, Comment No. C0013, Docket No. 78N-0301, Dockets Management Branch.

D. Comment on Testing of External Analgesic Drug Products

14. One comment suggested several methods for testing the actions, effects, and efficacy of external analgesic ingredients. These included a laboratory animal study utilizing trolamine salicylate tagged with Carbon-14 to determine the degree of local

penetration and distribution of this ingredient and developing a model to study the effects of topically applied trolamine salicylate on local tissue prostaglandin levels. In addition, the comment suggested a method of testing external-analgesic ingredients in humans that is detailed in a published study and involves inducing muscle soreness by a controlled amount of exercise and measuring the bioelectrical activity of the muscle by electromyography before and after external analgesic use to determine muscle soreness and the extent of drug activity (Ref. 1).

In the Federal Register of September 29, 1981, (49 FR 47740), the agency published a policy statement that included procedures for the submission and review of proposed testing protocols, for agency meetings with industry or other interested persons, and for agency communications on submitted test data and other information. Under this policy, the agency provides consultation on protocols or testing guidelines, but these communications are not included in the administrative record for the related OTC drug monograph unless they directly influence an agency decision on a particular matter in the monograph or provide the substantiation for the agency's decision on that matter. For example, a protocol or test guideline would not normally become part of the administrative record, but the results of the study would be included in the administrative record. The testing methods suggested by the comment do not influence the agency's decision on the Category III status of trolamine salicylate; therefore, they will not be discussed further in this document.

Reference

- (1) White, J. R., and J. N. Sage, "Topical Analgesic on Induced Muscular Pain," *Physical Therapy*, 50:166-172, 1970.

E. Comments on Labeling of External Analgesic Drug Products

15. Several comments objected to the agency's policy of specifying a limited list of terms as the only permissible indications for external analgesic products. One of the comments argued that it is improper and inappropriate to legislate the use of words and phrases through a rulemaking. One comment stated that the agency lacks statutory authority to prescribe exclusive lists of terms. All the comments requested that the final monograph allow the use of alternative or additional labeling terms that are truthful, accurate, not

misleading, and intelligible to the consumer.

During the course of the OTC drug review, the agency has maintained that a monograph describing the conditions under which an OTC drug will be generally recognized as safe and effective and not misbranded must include both specific active ingredients and specific labeling. (This policy has become known as the "exclusivity rule.") The agency's position has been that it is necessary to limit the acceptable labeling language to that developed and approved through the OTC drug review process in order to ensure the proper and safe use of OTC drugs. The agency has never contended, however, that any list of terms developed during the course of the review literally exhausts all the possibilities of terms that appropriately can be used in OTC drug labeling. Suggestions for additional terms or for other labeling changes may be submitted as comments to proposed or tentative final monographs within the specified time periods or through petitions to amend monographs under § 330.10(a)(12). For example, the labeling proposed in this tentative final monograph has been expanded and revised in response to comments received.

During the course of the review, FDA's position on the "exclusivity rule" has been questioned many times in comments and objections filed in response to particular proceedings and in correspondence with the agency. The agency has also been asked by The Proprietary Association to reconsider its position. To assist the agency in resolving this issue, FDA conducted an open public forum on September 29, 1982 at which interested parties presented their views. The forum was a legislative type administrative hearing under 21 CFR Part 15 that was held in response to a request for a hearing on the tentative final monograph for nighttime sleep-aids and stimulants (published in the Federal Register of June 13, 1978; 43 FR 25544). The agency's final decision on this issue will be announced in the Federal Register following conclusion of its review of the material presented at the hearing.

16. One comment disagreed with the Panel's recommendations that inactive ingredients and the quantity of the ingredient be listed in the labeling of OTC external analgesic drug products. The comment argued that a list of inactive ingredients would be meaningless to all but a few consumers and that such a list might overemphasize the importance of the

inactive ingredients, obscure more meaningful information such as warnings or directions for use, and be more confusing than helpful. The comment also stated that if the quantity of the inactive ingredients had to be listed there would be an additional problem of changing the labels whenever the quantity of an inactive ingredient is changed.

The agency agrees with part of the Panel's recommendation. The Federal Food, Drug, and Cosmetic Act does not require the identification of all inactive ingredients in the labeling of OTC drug products. Section 502(e) (21 U.S.C. 352(e)) does require disclosure of active ingredients and of certain ingredients, whether included as active or inactive components in a product. Although the inclusion of all inactive ingredients in OTC drug product labeling is not required, the agency urges manufacturers to list all inactive ingredients voluntarily, as suggested by the Panel. Consumers with known allergies or intolerance to certain ingredients could then select products with increased confidence of safe use.

With regard to listing the quantity of inactive ingredients, section 502(e) (21 U.S.C. 352(e)) limits the requirement for stating the quantity of active ingredients in OTC labeling to those specifically named in that section. The agency cannot require listing of the quantity of any ingredient, whether active or inactive, in OTC drug products, except those designated in the act.

17. One comment questioned the Panel's qualifications and competence to evaluate and judge what message was being communicated to the consumer, expressed in lay terms, in its recommended labeling. The comment stated that in many cases the words and phrases recommended by the Panel were based on the Panel's own perceptions as to what the terms communicate to the consumer and that the Panel did not provide any documentation, surveys, etc., to support its findings.

Since its inception, the OTC drug review has focused on developing labeling of OTC drug products that can be understood by the average consumer. While the agency acknowledges that professional experience in mass communication was not a criterion for participation in the OTC drug advisory review panels, the clinical background of the physicians, pharmacists, and other health professionals on each panel involved direct experience with patients and an awareness of the terms used by them to refer to their symptoms. In addition to members of the scientific

and medical communities, each panel included representatives from industry and consumer groups and thus had access to the experience of these groups in mass communication of medical terminology. Finally, any citizen interested in doing so could participate in the OTC drug review by presenting views at panel meetings, and, now that the panels have concluded their reviews, by commenting on advance notices of proposed rulemaking or by commenting or objecting to tentative final monographs proposed by the agency. A number of changes in the Panel's recommended labeling of external analgesic products have been incorporated into the agency's proposed labeling as a result of comments received. The agency urges anyone having suggestions for making the labeling language used in the external analgesic final monograph more understandable to the average consumer to submit these suggestions in comments responding to this document. After a final monograph for external analgesic drug products is issued, such suggestions may be made in the form of a petition to amend the monograph according to the procedures described in 21 CFR 10.30.

18. One comment to the advance notice of proposed rulemaking for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products (published in the Federal Register of September 9, 1976; 41 FR 38312) requested that OTC external analgesic drug products be included in the table at 41 FR 38320 that listed specific symptoms and the corresponding pharmacologic groups of drugs for the treatment of these symptoms. The comment suggested that item 8 of the table, "Generalized aching," be expanded to include the Category I labeling indications for topical analgesics, counterirritants, and rubefacients recommended by the Topical Analgesic Panel.

The agency does not agree that external analgesic drug products are suitable for inclusion in item 8 of the Cough/Cold Panel's table because this inclusion would imply that external analgesics should be labeled for relief of symptoms of aching due to common cold. The agency is not aware of any data, nor were any submitted, indicating that these products are effective in relieving symptoms of aching due to the common cold. If such data are submitted in the future, the agency will reconsider this claim.

19. One comment suggested that the claims not reviewed by the Topical Analgesic Panel but considered by other panels (e.g., "antiseptic," "fungistatic for

athlete's foot") and claims deferred to other panels (e.g., "pain due to hemorrhoids," "piles,") should not have been listed under Category II labeling in paragraphs (d) and (e) (44 FR 69845), but should have been left unclassified, pending classification by the appropriate panels.

The agency agrees with the comment that the claims under (d) and (e) at 44 FR 69845 should not be classified in Category II in the rulemaking for external analgesic drug products. These claims have been deferred to other panels and are covered in separate rulemaking proceedings. With the exception of claims relating to diaper rash, these claims will no longer be considered in this rulemaking. Drug products for the treatment of diaper rash were reviewed by the Advisory Review Panel on OTC Miscellaneous External Drug Products, which recommended that some of the ingredients in those drug products be evaluated in the external analgesic rulemaking. As noted above the Federal Register of September 7, 1982 (47 FR 39412) included a notice of reopening of the administrative record to include the Miscellaneous External Panel's statement on drug products for the treatment of diaper rash. The agency will address the use of external analgesic active ingredients for the treatment of diaper rash in this rulemaking in a future Federal Register publication.

20. One comment stated that there is no evidence that the term "external analgesic," the Panel's recommended statement of identity, is more informative to consumers than other terms such as "topical analgesic" or "pain relieving ointment." The comment suggested that the latter terms be allowed in addition to "external analgesic."

The agency agrees that the terms referred to by the comment would be as informative to consumers as the Panel's recommended statement of identity. Therefore, the agency is proposing the following alternative statements of identity in § 348.50(a)(1): "The labeling identifies the product as an 'external analgesic,' 'topical analgesic,' or 'pain relieving (insert dosage form, e.g., cream, lotion, or ointment).'"

21. Several comments requested that the statement of identity for OTC hydrocortisone products be changed from "antipruritic" to "anti-itch." The comments argued that "antipruritic" is a technical term that would not be understood by most consumers and that the term "anti-itch" would be more meaningful.

The agency agrees with the comments that the term "antipruritic" may not be

well understood by many consumers and, if used, should be associated with a nontechnical term. Accordingly, the following statements of identity are being proposed for hydrocortisone products in § 348.50(a)(2): "antipruritic (anti-itch)," "anti-itch," and "antipruritic (anti-itch)" or "anti-itch" followed by a description of the dosage form, e.g., "anti-itch cream."

22. One comment stated that hydrocortisone is probably not effective for the relief of itching due to insect bites, or for contact dermatitis due to poison ivy, oak, and sumac and that more potent corticosteroids are usually required for these problems. Another comment questioned "whether consumers can accurately diagnose contact 'dermatitis' due to 'poison oak' or 'poison sumac'" and added that the labeling terminology should be revised.

The agency is aware that severe skin inflammation caused by poison ivy does not respond to topically applied hydrocortisone, and that even the stronger halogenated steroids are not effective when used topically in such instances. Severe poison ivy often requires systemic steroid therapy. Topically applied hydrocortisone is also not effective in relieving severe reactions to insect bites. However, the itching due to mild poison ivy and to normal reactions to insect bites is relieved by topical hydrocortisone at OTC strength (Refs. 1, 2, and 3). The agency believes that the words "temporary" and "minor" in the indications for hydrocortisone are sufficient to alert consumers to the appropriate use of this ingredient. The agency is proposing deletion of the word "dermatitis" from the OTC hydrocortisone label because this word is not apt to be readily understood by consumers. This word is suitable for professional labeling, and a closely related term, "dermatoses," is included under "Indications and Usage" in the agency's class labeling guideline for topical corticosteroids (Ref. 4). Manufacturers should follow this guideline in developing professional labeling for hydrocortisone drug products. The terms "poison oak" and "poison sumac" are retained in the proposed OTC labeling because these plants and the rash and itching they cause are familiar to consumers who live in areas in which the plants are found.

References

- (1) Letter from A. M. Kligman to C. C. Evans, FDA, November 3, 1980, Docket No. 78N-0301, Dockets Management Branch.

- (2) Fisher, A. A., "Contact Dermatitis," 2d Ed., Lea and Febiger, Philadelphia, pp. 264-265, 1973.

- (3) Domonkos, A. N., H. L. Arnold, and R. E. Odom, "Andrews' Diseases of the Skin," 7th Ed., W. B. Saunders Co., Philadelphia, p. 559, 1982.

- (4) Food and Drug Administration, "Topical Corticosteroids Class Labeling Guideline," Docket No. 81D-0274, Dockets Management Branch.

23. One comment stated that, because the claim "relief of cuts, scratches, abrasions, wounds, etc.," is similar to indications recommended by the Panel in § 348.50(b)(2), the Panel must have inadvertently included this claim under Category II labeling at 44 FR 69844-69845.

The Panel concluded that the above claim was confusing and meaningless to consumers because external analgesic drug products relieve the pain of cuts, scratches, abrasions, wounds, etc., but do not provide "relief of cuts" The agency concurs with the Panel's Category II classification of this claim.

24. One comment argued that there is a need for a distinction between the labeling of topical analgesic and topical anesthetic ingredients. The comment stated that the Panel had differentiated between analgesics and anesthetics through distinct definitions in § 348.3(d) and (e), by establishing separate subgroups of external analgesics (44 FR 69786), and in its combination policy. The comment pointed out that topical analgesics depress cutaneous sensory receptors without necessarily abolishing other sensations (i.e., cause a partial blocking of subcutaneous terminal nerve endings), whereas topical anesthetics completely block pain receptors, resulting in a sensation of numbness. The comment concluded that consumers should be informed of these distinctions and suggested the following examples of wording that could be used in the indications for topical anesthetic ingredients: "complete temporary relief" "completely blocks" "temporarily stops" "completely stops"

The agency does not agree that there is a need for a distinction between the labeling of topical analgesic and topical anesthetic products. In use, the effect of topical anesthetics is indistinguishable from the effect of topical analgesics. Topical anesthetics are theoretically capable of completely blocking pain receptors, but factors may affect the penetration of topical anesthetics through the skin and prevent complete blocking of the subcutaneous pain receptor site. Some of the factors affecting penetration of topical